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Autophagy inhibitors and inducers as modulators of trimethyltin toxicity in neurons and glial cells

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Trimethyltin (TMT) is a triorganotin compound which determines neurodegeneration of specific brain areas particularly damaging the limbic system. Organotin compounds are used as heat stabilizers in polyvinyl chloride polymers, industrial and agricultural biocides, and industrial catalysts in chemical reactions.

The mechanism underlying TMT selective tissue-specific pattern of cellular damage is not completely known unless a correlation exists between TMT toxicity and the expression of stannin, a highly-conserved protein mainly localized within mitochondria. Ultrastructural studies performed on samples obtained from the brain of humans and rodents intoxicated with TMT describe increased number of lysosomes and big vacuoles suggestive of altered autophagy.

Our results show that autophagy inhibitors added to TMT dramatically increased the toxicity of this compound both in hippocampal and cortical neurons. Conversely, autophagy inducers such as rapamycin and lithium prevent the neurotoxicity of TMT. Due to its diverse targets, the action of lithium may be complex and its neuroprotective property is sometimes controversial. Our data show that in acute treatment experiments hippocampal and cortical neurons behave quite differently when challenged with lithium. The neuroprotective effect of lithium acutely administered against TMT in hippocampal but not in cortical neurons can be completely reverted by an excess of inositol and is possibly related to the inactivation of inositol monophosphatase, a key regulator of autophagy. Lithium is also effective in preventing TMT toxicity in astrocyte cell cultures in a range of concentrations of 0.2-4 mM.

Keywords: neurotoxicity, lithium, autophagy, astrocyte